clarify that the invention relates to methods for forming cross-over proteins through the ligation of the C-terminal amino acid residue of a peptide segment of a first protein with the N-terminal amino acid residue of a peptide segment of a second protein. Support for such amendments can be found throughout the specification (see, for example, page 29, lines 15-18). No new matter has been introduced by the requested amendments.

II. Information Disclosure Statement

The form PTO-1449 accompanying the Official Action issued with respect to the parent application indicated that certain references cited and provided by Applicants could not be located in the Examiner's files. Applicants have previously submitted duplicate copies of these documents, and have requested that they be considered and made of record in the prosecution of the present application. The Examiner is respectfully requested to initial the previously enclosed Form 1449 to indicate such consideration of these documents.

III. The Objection to the Specification

The specification has been objected to in light of the recitation of a serial number without listing the corresponding application series number. Applicants have amended the specification to provide the relevant application series number, and respectfully submit that such action fully addresses the Examiner's concerns. Applicants submit that the objection may therefore be properly withdrawn.

IV. The Rejections Pursuant to 35 U.S.C. 112, First Paragraph

Claims 33 and 34 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter that is not described in the specification in a manner that would reasonably convey to one of ordinary skill that the inventors were in possession of the invention at the time the application was filed. Specifically, the Examiner has suggested that the requested amendment involving different *families* of parent proteins (rather than

different proteins) constitutes new matter. Applicants respectfully traverse and request reconsideration.

Applicants respectfully submit that the specification provides clear evidence that the inventors were in possession of the inventions of claims 33 and 34 at the time the application was filed. In this regard, Applicants respectfully draw the Examiner's attention to the fact that original claim 35 was drawn to the embodiment of claim 32 in which the parent protein molecules were of the same family of protein molecules. Thus, when claims 35 and 32 are read together, those of ordinary skill would have concluded that claim 32 was drawn to both the embodiment of the invention in which the parent protein molecules are of the same family of protein molecules as well as the embodiment of the invention in which the parent protein molecules are of different protein molecules. Such a conclusion would have been reinforced by the disclosure at page 8, lines 9-12, that the first and second proteins preferably [*i.e., not necessarily*] are members of the same family of protein molecules. The invention, as filed, thus evidences that the inventors contemplated that different protein molecules be employed, and that such different protein molecules could be members of different classes of proteins.

Accordingly, Applicants respectfully submit that the rejection of claims 33 and 34 under 35 U.S.C. 112, first paragraph may be properly withdrawn.

Claims 28-36 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter that is not described in the specification in a manner that would reasonably convey to one of ordinary skill that the inventors were in possession of the invention at the time the application was filed. Specifically, the Examiner has suggested that the specification fails to provide sufficient written description to support a genus of cross-over proteins which are devoid of sequence length, amino acid content, specific biological function as alleged to be produced by the currently claimed method of ligating

one or more first proteins with one or more second proteins. Applicants respectfully traverse and request reconsideration.

The Examiner has suggested that support for this conclusion can be found in *University of California v. Eli Lilly & Co.* ("*Lilly*") and in the "Guidelines for Examination of Patent Applications," published at 1242 OG 168-178. Applicants respectfully disagree.

Applicants respectfully submit that the Examiner has erred in applying the "Guidelines for Examination of Patent Applications," published at 1242 OG 168-178. Applicants respectfully draw the Examiner's attention to the fact that the present invention involves a *method of forming* a molecule (a "cross-over protein" by combining peptide segments derived from different proteins). As the Examiner will recall, in *Lilly*, the patentee attempted to obtain *composition* claims that were not merely generically drawn to insulin-encoding polynucleotides, but that attempted to literally recite every possible species of insulin-encoding polynucleotide. The Federal Circuit held that the patentee had not complied with the written description requirement, and could not obtain claims that would literally recite an untold number of *compositions* in light of the disclosure. Thus, the issue in *Lilly* is clearly stated in the Guidelines for Examination of Patent Applications," published at 1242 OG 168-178:

> "Eli Lilly explains that a chemical compound's name does not necessarily convey a written description of the n[ucleic] a[cid] chemical compound, particularly when a genus of compounds is claimed. Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1405. The name, if it does no more than distinguish the claimed genus from all others by function, does not satisfy the written description requirement because 'it does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.' Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. Thus, Eli Lilly identified a set of circumstances in which the words of the claim did not,

without more, adequately convey to others that applicants had possession of what they claimed."

Applicants respectfully submit that the issues of concern in *Lilly* are thus irrelevant to the presently claimed invention.

Applicants note the Examiner's quotation of caselaw that a description of an invention involving a chemical genus requires a precise definition such as by structure, formula or chemical name of the claimed subject matter sufficient to distinguish it from other materials. Contrary to the Examiner's suggestion, no caselaw holds that an Applicant must set forth every possible combination and permutation of amino acid residues for such segments in order to obtain a claim reciting the word "protein." Clearly, claims reciting the word "protein" are routinely granted irrespective of whether the sequence length, amino acid content, or specific biological function are recited. No caselaw holds that an Applicant seeking a method claim containing the word "protein" must describe every possible combination and permutation of amino acid residues that can be synthesized using that *method*. Applicants respectfully submit that the rejection of claims 28-36 under 35 U.S.C. 112, first paragraph may be properly withdrawn.

V. The Rejections Pursuant to 35 U.S.C. 112, Second Paragraph

Claims 28-36 have been rejected pursuant to 35 U.S.C. 112, second paragraph as being indefinite. The Examiner has rejected claim 28 in light of the recitation therein of the word "parent." Applicants have amended claim 28, to delete the term "parent," and respectfully submits that such action fully addresses the Examiner's concerns. Applicants respectfully submit that the rejection may thus now be properly withdrawn.

The Examiner has additionally rejected claims 28 and 32, and their dependent claims, in light of the recitation therein of the terms "N-terminal peptide" and "C-terminal peptide." Specifically, the Examiner has expressed a concern that those of ordinary skill would not know whether such terms refer to the "first" or "second protein,

or to the ultimate position of the peptide in the cross-over protein. The Examiner has additionally suggested that the claims are confusing where more than one N-terminal or C-terminal peptide is involved. The Examiner has additionally suggested that those of ordinary skill would consider the term "N-terminal peptide segment" or "C-terminal peptide segment" as referring to a single amino acid and not a segment of amino acids. The Examiner has additionally rejected the terms "N-terminal peptide segment" and "C-terminal peptide segment" as not being defined by the claims. In this regard, the Examiner has questioned whether those of ordinary skill would know what these terms meant (i.e., "what number of amino acids constitute an N-terminal peptide segment"). The Examiner has also rejected claims 28 and 32 in light of an alleged redundancy with respect to the recitation of "having a C-terminus and an N-terminus."

Applicants respectfully traverse these rejections and request reconsideration in light of the requested amendments to the claims. Applicants respectfully submit that those of ordinary skill would, in light of the specification, readily comprehend that the invention concerns methods of forming proteins by combining together discrete peptide segments each of which contains an N-terminal amino acid residue and a C-terminal amino acid residue. The claims as amended now clarify how these segments are ligated to one another, and omit the N-terminal and C-terminal segment language that the Examiner considered confusing. Applicants respectfully submit that such action fully addresses the Examiner's concerns, and that the above-stated rejections may now all be properly withdrawn.

The Examiner has rejected claims 30, 33-35, and their dependent claims in light of the recitation of the terms "same (different) family of protein molecules," which is advised to be undefined and to render the claims indefinite. The Examiner has suggested that the application fails to indicate what characteristics distinguish one family of proteins from another. Applicants respectfully traverse and request reconsideration.

Applicants respectfully submit that the term "family of proteins" is a term of art that would be readily understood by those of ordinary skill. In this regard, those of ordinary skill will know of multiple databases of protein families (e.g., http://pfam.wustl.edu/, http://www.expasy.ch/prosite/; http://www.public.iastate.edu/~pedro/p_families.html; http://www.infobiogen.fr/services/deambulum/english/proteins.html; etc.). The term "protein family" is frequently used in the specification and claims of U.S. Patents (see, for example, U.S. 6,331,388; U.S. 6,326,150; U.S. 6,294,330; U.S. 6,048,530; U.S. 5,993,865; U.S. 5,972,385; U.S. 5,961,979; U.S. 5,948,428; U.S. 5,916,870; U.S. 5,854,207; U.S. 5,827,838; U.S. 5,827,685; U.S. 5,795,721; U.S. 5,741,635; U.S. 5,731,166). As additional evidence that these terms would be readily understood by those of ordinary skill, Applicants conducted a search of the NCBI Pub-Med database for articles that used the term "protein family" or "protein families." A copy of the search report is enclosed. As the Examiner will note – *in a single year*, 1997 – over 9,000 published articles used these terms. Over 1,000 of these articles are indicated to be review articles. In light of such evidence, Applicants respectfully submit that the terms "protein family" or "protein families are not indefinite, and that those of ordinary skill would readily understand their meaning. Applicants accordingly respectfully submit that the above-discussed rejection may be properly withdrawn.

VI. The Rejections Pursuant to 35 U.S.C. 102

A. The Rejections Of Claims 28-31 In Light Of Canne *et al.* and Dawson *et al.*

The Examiner has rejected claims 28-31 as anticipated pursuant to 35 USC § 102(b) in light of Canne *et al.* (J. Am. Soc.). Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

The claims of the present invention have been amended to more clearly describe the nature of the ligation reaction as involving the ligation of N-terminal and C-terminal peptide segments derived from different proteins to form a cross-over protein having an

N-terminus and a C-terminus. As the Examiner will appreciate, the presently claimed invention is neither disclosed nor suggested by the cited Canne *et al.* reference (J. Am. Soc.). In this regard, the Examiner will appreciate that the cMyc-Max molecule described by Canne *et al.* is formed via an ***C-terminal to C-terminal ligation*** of cMyc and Max peptide domains (see page 2999, first sentence of paragraph bridging left and right columns), and that the resulting ligation product thus possesses ***two N-termini and no C-terminus***. Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the Canne *et al.* reference may be properly withdrawn.

The Examiner appears to have also rejected claims 28-31 as anticipated pursuant to 35 USC § 102(b) in light of Dawson *et al.* (Science), although no basis for such rejection was provided. Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

As the Examiner will appreciate, the Dawson *et al.* reference fails to teach or suggest the invention of producing cross-over proteins that are composed of peptide segments from ***different*** proteins. In this regard, Applicants have respectfully drawn the Examiner's attention to the experimental methods outlined at page 777 of the Dawson *et al.* document, which clarify that the document discloses the ligation of peptide sub-segments of the ***same*** protein (IL-8). Accordingly, Applicants respectfully submit that any rejection of the claims in light of the Dawson *et al.* reference may be properly withdrawn.

B. The Rejections Of Claims 28-30 In Light Of Clark-Lewis *et al.*

The Examiner has rejected claims 28-30 as anticipated pursuant to 35 USC § 102(b) in light of Clark-Lewis *et al.* (J. Biol. Chem.). Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

Applicants respectfully submit that the presently claimed invention is not anticipated in light of Clark-Lewis *et al.* (J. Biol. Chem.). The Clark-Lewis *et al.* (J. Biol.

Chem.) reference describes a method for forming cross-over proteins (i.e., the use of solid phase amino acid synthetic chemistry) that is distinct from the ***method being presently claimed*** (i.e., a process involving the **chemoselective** chemical ligation of complementary reactive groups present at the N-terminus and C-terminus of two peptides). As the examiner will appreciate, the present claims are thus drawn to ***methods of production*** that are neither taught nor suggested by the methods or compositions disclosed in the cited reference. Accordingly, the rejection of claims 28-30 in light of Clark-Lewis *et al.* (J. Biol. Chem.) may be properly withdrawn.

VII. The Rejections Pursuant to 35 U.S.C. 103(a)

A. The Rejections Of Claims 28-31 In Light Of Publications of Canne *et al.* and Dawson *et al.*

The Examiner has rejected claims 28-31 as obvious pursuant to 35 USC § 103(a) in light of Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science). Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

The Canne *et al.* publication has been discussed above. The claims, as presently amended, more clearly describe the nature of the ligation reaction as involving the chemoselective chemical ligation of N-terminal and C-terminal peptide segments derived from different proteins, to form a cross-over protein having an N-terminus and a C-terminus. In light of such amendments, it is respectfully submitted that the cited Canne *et al.* publication fails to render the invention obvious

The Examiner has noted that the cited Canne *et al.* reference cites the Science publication of Dawson *et al.* with respect to native chemical ligation, and has suggested that such citation would have rendered the present invention obvious. Applicants respectfully submit that such an interpretation fails to address the actual teachings of these references. As discussed above, Applicants submit that the Canne *et al.* reference

teaches the ***C-terminal to C-terminal ligation*** of two peptide domains (see page 2999, first sentence of paragraph bridging left and right columns). Applicants submit that the Dawson *et al.* reference teaches the use of native chemical ligation to synthesize a "non-crossover" protein.

Applicants respectfully submit that the references cannot be combined to suggest the present invention. The citation of the Dawson *et al.* reference in the Canne *et al.* reference is intended to show the use of an alternative, not a conjunctive, chemical synthesis approach. In this regard, Applicants respectfully submit that the true teaching of the Canne *et al.* reference is provided at page 2999 of the Canne *et al.* reference:

> "The synthesis of functional protein analogues containing unnatural backbone elements represents an important conceptual breakthrough that demonstrates that we need not be restricted to the formation of native peptide bonds [*i.e., such as the peptide bonds taught by Dawson et al.*] in order to have a biologically active protein."

Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the cited Canne *et al.* reference (alone or in combination with the cited Dawson *et al.* reference) may be properly withdrawn.

B. The Rejections Of Claims 28-36 In Light Of Publications of Canne *et al.*, Dawson *et al.* and Pavia *et al.*

The Examiner has rejected claims 28-31 as obvious pursuant to 35 USC § 103(a) in light of Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science), and further in light of Pavia *et al.* (Bioorganic Medicinal. Chem. Lett.). The Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science) references are discussed above. The cited Pavia *et al.* reference is stated to teach the use of combinatorial synthesis strategies in drug

discovery. Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

Applicants respectfully submit that the failure of the cited Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science) references to render the present invention obvious (see discussion above) is not remedied by the cited Pavia *et al.* reference. Significantly, none of the multiple synthetic approaches discussed in the Pavia *et al.* reference concerns the joining, by any means or in any orientation, of peptide domains of different proteins to form a library of cross-over proteins. Applicants respectfully submit that the cited Pavia *et al.* reference provides no more than a general review of combinatorial chemistry methods unrelated to those of the present invention. As such, the reference, alone or in combination with the cited Canne *et al.* and Dawson *et al.* references, is insufficient to render the present claims obvious.

Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the cited Canne *et al.*, Dawson *et al.*, and Pavia *et al.* references may be properly withdrawn.

C. The Rejections Of Claims 28-30 and 32-35 In Light Of Publications of Clark-Lewis *et al.* and Pavia *et al.*

The Examiner has rejected claims 28-30 and 32-35 as obvious pursuant to 35 USC § 103(a) in light of Clark-Lewis *et al.* (J. Biol. Chem.) and Pavia *et al.* (Bioorganic Medicinal. Chem. Lett.). The cited Pavia *et al.* reference is discussed above. The Clark-Lewis *et al.* reference is stated to disclose the formation of cross-over proteins that comprise fragments from two different proteins. Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

Applicants respectfully submit that the cited Clark-Lewis *et al.* reference concerns only the use of t-butoxycarbonyl chemistry and automated solid-phase methods to synthesize proteins amino acid by amino acid in the classic Merrifield manner (see, page

16076, and Clark-Lewis *et al.*'s citation to Reference No. 28). Applicants respectfully submit that the cited Clark-Lewis *et al.* reference neither teaches nor suggests the chemoselective chemical ligation of functional protein domains of different proteins presently being claimed by Applicants. Applicants submit that the cited Pavia *et al.* reference (see discussion above) fails to remedy this deficiency, since the reference provides no teaching relevant the production of cross-over proteins by chemoselective chemical ligation.

Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the cited Clark-Lewis *et al.* and Pavia *et al.* references may be properly withdrawn.

VIII. The Non-Statutory Double Patenting Rejections

The Examiner has rejected claims 28-36 under the judicially created doctrine of obviousness-type double patenting in light of U.S. Patents No. 6,184,344 and 6,326,468 in view of the above-discussed Canne *et al.* reference, alone or in combination with the cited Pavia *et al.* reference.

In the interest of advancing the prosecution of the present application, and not as an acquiescence to the merits of the Examiner's arguments, Applicants respectfully advise that should the Examiner conclude that the amended claims define patentable and allowable subject matter that would have been obvious in light of the claims of the '344 and '468 patent, Applicants will terminally disclaim such portion of any patent that will issue on such claims that will extend beyond the terms of U.S. Patents No. 6,184,344 and 6,326,468. Applicants agree promptly to provide a Terminal Disclaimer upon notification of such allowable subject matter.

Having now fully responded to the issues raised by the Examiner, Applicants respectfully submit that the present application is now in condition for Allowance, and

earnestly solicit early notice of such favorable action. The Examiner is invited to contact the undersigned with respect to any issues regarding this application.

Respectfully Submitted,

Date: April 4, 2002

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Appendix A: The Nature of the Requested Amendments

To facilitate the Examiner's review of the patentability of the present invention, Applicant has reproduced below the specific nature of the requested amendments.

28. **[Three Times Amended]** A method of producing a cross-over protein that contains at least one peptide segment whose sequence is derived from a first protein and at least one peptide segment whose sequence is derived from a second protein**, wherein said second protein has an amino acid sequence that is different from that of said first protein, and wherein each of said peptide segments possesses an N-terminal amino acid residue and a C-terminal amino acid residue**, said method comprising:

ligating under chemoselective chemical ligation conditions (i) at least one [N-terminal] peptide segment comprising a functional protein module derived from said first protein, and (ii) at least one [C-terminal] peptide segment comprising a functional protein module derived from said second protein [having an amino acid sequence that is different from said first parent protein], wherein [said N-terminal peptide segment and said C-terminal peptide segments] **the C-terminal residue of said peptide segment derived from said first protein and the N-terminal residue of said peptide segment derived from said second protein** comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said [N-terminal] peptide segment**s** [and said C-terminal peptide segment] so as to produce a chemical ligation product comprising a cross-over protein [having a C-terminus and an N-terminus] **in which the C-terminal residue of the peptide segment derived from said first**

protein is ligated to the N-terminal residue of said peptide segment derived from said second protein.

29. **[Amended]** The method of claim 28 further comprising the step of [repeating said ligating one or more times] **conducting one or more additional ligations** with one or more **additional** [second] peptide segments**, each possessing an N-terminal amino acid residue and a C-terminal amino acid residue, wherein said additional peptide segments are** selected from the group consisting of [an N-terminal peptide segment and a C-terminal peptide segment] **a peptide whose C-terminal residue comprises a reactive group capable of chemoselective chemical ligation with a reactive group of an N-terminal residue of another peptide, and a peptide whose N-terminal residue comprises a reactive group capable of chemoselective chemical ligation with a reactive group of an C-terminal residue of another peptide.**

30. **[Three Times Amended]** The method of claim 28, wherein the first and second protein molecules from whose sequences said [N-terminal peptide(s) and said C-terminal peptide(s)] **peptides** are derived belong to the same family of protein molecules.

32. **[Three Times Amended]** A method of producing a cross-over protein library whose members contain [at least one peptide segment whose sequence is derived from a first protein and at least one peptide segment whose sequence is derived from a second protein] **two or more peptide segments, each segment possessing an N-terminal amino acid residue and a C-terminal amino acid residue, and wherein the peptide segments of said members are derived from**

two or more different proteins, said method comprising:

incubating [ligating] under chemoselective **ligation** reaction conditions a plurality of unique [N-terminal] peptide segments each comprising one or more functional protein modules derived from [said] **a member of a** first **set of** protein **molecules** and a plurality of unique [C-terminal] peptide segments each comprising one or more functional protein modules derived from **a member of** a second **set of** protein **molecules** [having an amino acid sequence that is different from said first protein, wherein said N-terminal peptide segments and said C-terminal peptide segments] **wherein the C-terminal residues of each of said peptide segments derived from said members of said first set of protein molecules and the N-terminal residue of each of said peptide segments derived from said members of said second set of protein molecules** comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said [N-terminal peptide segments and said C-terminal] peptide segments so as to produce a plurality of chemical ligation products comprising a plurality of unique cross-over proteins**, wherein, for** each [having a C-terminus and an N-terminus] **such cross-over protein, the C-terminal residue of a peptide segment derived from a member of said first set of protein molecules is ligated to the N-terminal residue of a peptide segment derived from a member of said second set of protein molecules**.

33. [**Twice Amended**] The method of claim 32, wherein said plurality of [N-terminal] peptide segments **derived from members of said first set of protein molecules** are obtained by cross-over ligation of two or more different families of

protein molecules.

34. [**Twice Amended**] The method of claim 32, wherein said plurality of [C-terminal] peptide segments **derived from members of said second set of protein molecules** are obtained by cross-over ligation of two or more different families of protein molecules.

35. [**Three Times Amended**] The method of claim 32, wherein [the] **said** first and second protein molecules [from whose sequences said N-terminal peptide(s) and said C-terminal peptide(s) are derived] belong to the same family of protein molecules.

Amendments to the Specification:

The paragraph beginning at page 19, line 25 and continuing to page 20, line 9 has been amended as follows:

-- Assays of particular interest employ receptors provided by tissues or cell preparations, synthetic preparations and the like. Receptors of particular interest are lipid membrane-bound receptors generated by lipid matrix-assisted chemoselective chemical ligation as described in U.S. Patent Application Serial No. **09**/144,964. Screening for binding of a cross-over protein ligand comprising one or more chromophores to a target receptor is preferably performed in a FRET assay. Ligand binding can be measured by any number of methods known in the art for FRET analyses, including steady state and time-resolved fluorescence by monitoring the change in fluorescence intensity, emission energy and/or anisotropy, for example, through energy transfer from a donor moiety to an acceptor moiety of the FRET system. (See, e.g., Wu et al., Analytical Biochem. (1994) 218: 1-13). FRET assays allow not only distance measurements, but also resolution of the range of donor- to-acceptor distances. FRET also can be used to show that the ligand and/or target receptor exists alternately in a single conformational state, or with a range of donor-to-acceptor distances when in a different state, such as when bound to a ligand. More than one donor-acceptor pairing may also be included. --